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Congenital Disorders of Vitamin B_{12} Transport and Their Contributions to Concepts. II

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Congenital deficiencies of Transcobalamin II (TC II) and R binders of vitamin B_{12} (B_{12}, cobalamin, Cbl) have been described in several families. The deficiency of TC II exists as at least three variants. The deficiency of TC II is expressed by a profound megaloblastic pancytopenia during the first few weeks of life, but the serum Cbl is normal. In contrast, the deficiency of R binder is asymptomatic, tissues are replete in Cbl, but the serum Cbl is low. All of the R binder in the several body sources is under the same genetic control. Studies of the congenital deficiency of TC II suggest the following: (1) The function of TC II is the promotion of cell uptake of physiologic amounts of Cbl, which can also be accomplished by very large amounts of Cbl, and not in any intracellular process. (2) TC II is essential for the absorption, postabsorptive distribution, and recycling of TC II. (3) The metabolic consequences of TC II deficiency are expressed primarily in rapidly dividing cells probably because they are dependent upon the constant need for new Cbl.

The intent of this presentation is to point out what we have learned and have yet to learn about the clinical and fundamental aspects of cobalamin (Cbl, vitamin B_{12}) metabolism from the study of congenital defects of Cbl transport. In the original article of the same title of 1973 I included the disorders of intestinal transport [1]. Over the past decade there have been no important new observations or interpretations of the congenital defects of Cbl absorption, but there have been many significant developments in the field of Cbl plasma transport.

The established carriers and functions of the plasma system of man can be summarized briefly. As the Cbl is released from the intestinal carrier, intrinsic factor, it is bound to the most important plasma carrier, transcobalamin II (TC II). This specific, trace protein of plasma can carry about 1.0 ng of Cbl per ml but only about 10 percent of circulating TC II is actively carrying Cbl. When Cbl becomes bound to TC II *in vivo* the TC II-Cbl is rapidly delivered to specific receptors in many tissues. The TC II-Cbl is internalized followed by the release of the Cbl to be utilized further. Much of the evidence of the need for TC II in the recycling of Cbl will be given subsequently. Only about one-fourth of the circulating Cbl is carried by TC II. The rest is bound to a glycoprotein known as R binder. R binder is found in granulocytes and several body fluids including milk, gastric juice, bile, saliva, and tears. The polypeptide part of the molecule is the same for R binder of any source, but the car-

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bohydrate portion, especially the sialic acid, varies greatly. There is no known function of R binder but in experimental models that R binder of low sialic acid content will deliver Cbl to receptors for asialoglycoproteins which are restricted to hepatocytes. These receptors are distinct from those receiving TC II-Cbl; TC II is not a glycoprotein. The Cbl released from the R binder can then return to the body pool. As for many body proteins, there are genetic defects of the proteins of the plasma Cbl transport system, TC II, and R binder. A TC II-Cbl receptor defect has not been described, but we are currently evaluating a patient in which this is a possibility. There are congenital defects of intrinsic factor (IF) and of the ileal receptor of IF-Cbl, transport proteins of the gut, the compartment that precedes the circulation. There are also genetic defects of the Cbl metabolism of cells, the targets of plasma transport.

Genetic polymorphism has been described for both transcobalamin II (TC II) and the R type binder of Cbl [2–4]. Determination of TC II by a single locus with four or five functionally normal codominant alleles was reported in two simultaneous and independent investigations [2,3]. Gene frequencies have been determined for different populations [2,5]. Unfortunately a common nomenclature for these electrophoretically distinct alleles has not yet emerged. The congenital deficiency of TC II, where there is no binding of Cbl to a TC II, is expressed by a "null" allele as would be expected since the technique of identification of the allele is dependent upon binding of radioactive Cbl to the TC II [2]. However, a genetically determined TC II which bound Cbl, but was otherwise nonfunctional, was expressed by a sixth allele [6]. Similar polymorphism pertains to the determination of R binder, although only two alleles have been identified [4]. Significantly, the same locus and same alleles determine the R binder of several body tissues and fluids [4]. This observation was predicted from the syndrome of congenital deficiency of R binder where R binder was deficient in all body sources [7].

There have been no new reports of the congenital deficiency of R binder, although there have been additional studies of the original family [8]. Two fundamentally important observations were confirmed: (1) The absence of an R binder that would bind Cbl was universal among five sources expected to contain R binder, and (2) there were no identifiable clinical consequences of the deficiency. In fact, the liver of a subject homozygous for the defect contained normal amounts of Cbl, and both liver and serum contained normal proportions of the several forms of Cbl (unpublished data).

Reports of the congenital deficiency of TC II have in contrast blossomed, although the syndrome is by no means common. Deficiency of TC II is severely symptomatic, calling attention to its presence while that of R binder is encountered only by chance when a person free of evidence of Cbl deficiency is found to have a low serum Cbl. At this writing, 14 living cases, almost evenly divided between the sexes and representing 13 families, are known to me. Seven cases have been reported [9–14], Table 1. The reported cases are thoroughly representative of all cases with which I have had some contact. Six of the reported cases and six of the others represent the most common variant, which is characterized [15] by (1) no measurable binding of Cbl *in vivo* or *in vitro* to TC II, (2) an either much-diminished or absent immunoreactive TC II. Clinically affected persons are homozygous for the allele expressed as a null by current methods [2,6]. Those heterozygous are partially deficient with one null allele. The second variant may not yet have been observed in the homozygous state. There is one reported case [13] which seems to be double

TABLE 1
Reported Cases of Congenital Abnormalities of Transcobalamin II

Patient and Ref.	Age at Onset	Cytopenia*	At Onset Ser. Cbl pg/ml	At Onset Ser. folate ng/ml	Transcobalamin II pg Cbl/ml By RIA (Total)	Transcobalamin II pg Cbl/ml Endogenous (Holo)	Transcobalamin II pg Cbl/ml UBBC (Apo)
Variant of nil TC II by RIA and no binding by TC II							
An.S. [9]	3.5 wk	P	267	20	<50	0	0
Am.S. [9]	5 wk	R, Pl	855	–	<50	0	0
A.B. [10]	3 wk+	P	400	–	nil	0	0
– [11]	9 d	R, Pl	350	–	–	–	0
N.A. [12]	2 mo	R	505	18	–	–	0
H.M. [20]	1 mo	P	–	–	nil	0	0
V.P. [14]	4–6 wk	P	N++	N++	nil	0	0
Variant of some TC II by RIA but no binding by TC II							
– [13]	6 wk	P	–	–	352	nil	<50
Variant of TC II by RIA and by binding but non functioning TC II							
C.B. [16]	12 yr	P	Age 34 >4,000	–	6,400	4,384	2,139

*P = Pan, R = Red Cells, Pl = Platelets
+After removal from protective environment
++ = Reported only as being normal
Radioimmunoassay (RIA) for TC II by laboratory of [13] for An.S. and Am.S. For A.B., H.M., V.P., and C.B. in laboratory of present author as well as holo TC II for An.S., Am.S., A.B., H.M., V.P., and C.B.

heterozygous for the classical allele expressed as no Cbl binding and nil immunoreactivity with an allele expressed as no binding, but an immunologically recognized TC II.

Because both variants express a non-functioning TC II, the subject is clinically TC II deficient. One of the unreported symptomatic cases also has an immunologically recognizable TC II, but the genetic pattern has not been fully worked out. The third variant, one living patient, is expressed as being probably homozygous for an allele conveying a TC II that binds Cbl *in vivo* and *in vitro*, reacts with anti human TC II but does not function [16]. Therefore, the subject is affected clinically but the binding of Cbl permits an analysis of the genetic pattern which seems to be a sixth allele [6]. Heterozygotes for all variants have been identified in both published and unpublished families, but, with one exception, have been asymptomatic. One person heterozygous for the null allele became megaloblastic at times of high alcohol intake [6].

The alleles expressing an abnormal TC II are distributed worldwide. The more common null allele has been detected in published cases whose national origin was American [9], Moroccan [10], British [11], Pakistani [12], and Spanish [14]. Unpublished cases have been observed in British (two), Japanese, and Australian families. The published case of the immunoreactive, but non-binding TC II was an American [13] and a similar unpublished case is from Malta. The binding but non-functioning TC II was observed in a Black American [16].

The combination of clinical expression of these congenital disorders of TC II and associated observations from the laboratory has revealed much about the function of this carrier of Cbl. Moreover, the unresolved questions have been put in sharper focus. The affected infant is born healthy and there is evidence, given below, that total body Cbl is adequate. The age of clinical onset was within the first six weeks of life in nine of 14 infants with the no binding type deficiency. In two more reported cases it was six to nine weeks [12,13]. In one well-observed case, not yet reported, it was three months, and in another, 16 months. This timing and abruptness of onset contrast with the later, slower clinical onset, usually in the second year, of Cbl deficiency owing to congenital defects of absorption [1]. The comparison reveals an important aspect of the function of TC II. It is essential for movement of Cbl from one tissue to another, although not necessarily from every tissue to every other tissue. Our earliest studies of TC II *in vivo* pointed to a function postabsorption, which happened to be the easiest phase to examine by techniques then available. Subsequently it was shown that TC II carried Cbl during recycling [17], as observations in the congenital deficiency of TC II confirm. The affected infant does not absorb Cbl, nor for a few months does he need to, yet some tissues appear to be severely depleted while others contain adequate amounts. The child with congenital malabsorption but adequate TC II on the other hand can postpone symptoms by freely moving his declining body Cbl, thus maintaining essential functions.

The nature of the symptoms is also revealing. Megaloblastosis has been universal and generally severe. Ulcerations of the buccal mucosa and combinations of vomiting and diarrhea were reported in all seven infants where a complete description is available. Thus, the Cbl deficiency of TC II affects cells of rapid Cbl turnover, permitting two possible interpretations. (1) TC II is an essential carrier for certain classes of cells only. (2) Other cell types also depend on TC II for efficient Cbl intake, but they are not as dependent on recurrent intake at short intervals as are rapidly dividing cells. The *absence* of certain manifestations may be equally significant; these will be discussed later.

The prevalence of infection in TC II deficiency has opened up a new field of study of Cbl metabolism. Each of eight cases for whom enough pertinent information has been recorded suffered infections, often multiple. Infection was the mode of death of two older untreated siblings of one child [10]. This child had, shortly after birth, an impaired ability to make immunoglobulins [18], an incapacity which was restored by treatment with large amounts of Cbl. Later a killing defect of his granulocytes was observed [19]. Cbl is needed for cell division, but some additional function is involved here because the impaired Ig response was seen in the first child at a time when there was no obvious abnormality of lymphocytes and in a second [20] during hematologic remission. The granulocyte killing defect was observed during otherwise successful therapy which had induced a hematologic remission [19]. It may be that these yet undefined requirements for Cbl by leukocytes are more sensitive than needs for Cbl in maintaining the number, size, and appearance of blood cells.

The intracellular biochemical lesion produced by a deficiency of TC II probably consists of a deficiency of the coenzymes of Cbl, Ado Cbl, and Me Cbl. The megaloblastosis, the response to pharmacologic amounts of Cbl, and the abnormalities of the dU suppression test [12] all support this thesis. It follows that a deficiency of TC

II leads to impaired activities of the Cbl-dependent methylmalonyl CoA mutase and the N^5 methyltetrahydrofolate:homocysteine methyltransferase of rapidly dividing cells. Somewhat disquieting, however, is the report that during a planned relapse of a TC II deficient child, the leukocytes oxidized propionate normally [21]. Another common consequence of impaired activity of the mutase is excretion of large amounts of methylmalonic acid (MMA) but excretion has been low in TC II deficiency. Urinary MMA was normal in two cases [10,21]. In another, MMA was normal at age one year during relapse, but was slightly increased during a planned relapse at age 17 years [11]. There was a distinct increase in a fourth case [12]. The more common forms of Cbl deficiency are also characterized by an increased urinary excretion of certain sulfur-containing amino acids. These precursors accumulate from the impaired activity of the Me Cbl dependent methyltransferase in any depletion of tissue Cbl and in the Cbl C and Cbl D mutants of Cbl metabolism, inherited disorders where the supply of Cbl is adequate, but synthesis of Me Cbl and Ado Cbl is impaired [22]. The excretion of homocystine and cystathionine is increased in Cbl deficiency caused by congenital defects of absorption [23] and in dietary deficiency of Cbl in infancy [24]. The cellular lesion of the deficiency of TC II should be the same with similar consequences but the excretion of the sulfur-containing amino acids is not increased [21], Table 2. Probably in the deficiency of TC II there is the *potential* for the same biochemical defects of many types of body cells as in other forms of Cbl deficiency or where activities of Cbl-dependent enzymes are impaired. In TC II deficiency, however, the expression is at first confined to rapidly dividing cells which contribute only a relatively small fraction of the total Cbl-dependent enzyme activities of the body. If the affected infant could survive without treatment the insult to his bone marrow and gut, he would then, as more tissues become depleted of Cbl, excrete increased amounts of MMA, homocystine, etc.

An alternate possibility is that not all tissues and/or Cbl processes are TC II dependent. Hepatocytes will take up Cbl bound to R type binder of relatively low sialic acid content via asialoglycoprotein receptors [26,27]. The Cbl is freed from the carrier and much returns to the circulation to be bound to TC II while some is excreted into the bile still bound to R binder [26]. Some is converted to coenzyme forms and incorporated into Cbl-dependent holo enzymes of the liver. Whether this occurs directly from the free Cbl released from the R binder, as presumably is possible, or whether it must first be bound to TC II is unknown. Should R Cbl make Cbl available to the liver in the absence of TC II, there may be enough body activity of

TABLE 2
Urinary Excretion of Products of Faulty Cbl Metabolism in mmol per mol creatinine

	Homocysteine	Mixed* Disulfide	Cystathionine	MMA
Cbl C Mutant⁺				
S.B. [25]	111–147	27–48	37–57	6,920
Nutritional Deficiency				
Age 6 mo [24]	96	52	175	8,980
Congenital Deficiency				
TC II [21]	Trace	–	8	< 1 mg/ml

*Of homocysteine and cysteine

⁺One typical case illustrated here. For variation among cases, see Table 1 of [25], Part II

Cbl-dependent enzymes to control, at least in part, the urinary excretion of MMA, etc. In the absence of any TC II, however, the Cbl would not be available to tissues other than the liver and could not prevent malfunction of Cbl-dependent processes in these tissues. The granulocytes of TC II deficient children do contain much apo R binder (unpublished data) which could carry free Cbl to the liver. Nothing is known about the release and fate of such binder *in vivo* or of its capacity to pick up free Cbl. We have examined the sera of eight TC II deficient persons and while there was holo R binder in the circulation, there was no binding capacity for added Cbl. Whereas R binder may effectively carry Cbl into hepatic cells, it is not the only source of hepatic Cbl. In the congenital deficiency of R binder there were normal amounts of Ado and Me Cbl in liver (unpublished data) and excretion of MMA was not increased [7,8]. Linnell et al. have suggested a defect in the synthesis of Ado Cbl but not of Me Cbl by the fibroblasts of TC II deficiency [28], although the observations of Berliner and Rosenberg [29] on total conversion of free Cbl by TC II deficient fibroblasts did not support this concept. The comparable depressions, and subsequent increases with treatment, of Me Cbl and Ado Cbl in granulocytes [19] and erythrocytes [30] are also contradictory.

Neither is the clinical expression of TC II deficiency as broad as that of other types of Cbl deficiency. Symptoms referable to the central and peripheral nervous systems are conspicuously absent. One reported patient [11] and two unreported have been at least mildly mentally retarded, but all were diagnosed rather late and had been given folic acid without concomitant Cbl. Mental retardation is not characteristic of simple Cbl deficiency, even of the types originating in early childhood, although there is one report to the contrary [31]. Again the differential rate of Cbl turnover may be the key. The cells of the nervous system may retain Cbl longer than those of the bone marrow and Cbl-deficient infants die or are treated before the cells of the nervous system become depleted. It is also possible that these cells are not TC II dependent. In spite of extensive knowledge about Cbl-dependent enzyme reactions of mammalian tissues, the precise defects responsible for either megaloblastosis or nervous system malfunction remain unknown. Regrettably, the experience with the deficiency of TC II has not helped resolve this mystery.

Why is not the megaloblastosis of Cbl deficiency or, for that matter, the effects on the nervous system, well developed *in utero*? Infants deficient in TC II are not anemic until a few weeks after birth. Even infants born of Cbl-deficient mothers do well for a time [24]. The four well-described infants with the Cbl C mutant [25,32], three of whom later were megaloblastic, required time to become anemic, although there was hypersegmentation of neutrophils at birth in one [25]. Where the mother is deficient in Cbl, the infant may get just enough to develop *in utero*. When the fetus does not have its own TC II, components of the maternal transport system may suffice. However, if the cells of the fetus lack the capacity to synthesize Me Cbl or Ado Cbl [22], how do the Cbl-dependent enzymes function? Perhaps Ado Cbl and Me Cbl from the mother combine with the respective fetal apo enzymes. Could, however, the infants' need for Cbl suddenly change at birth? The Cbl content of fetal tissues of such importance and mass as liver, kidney, heart, and brain is less than that of the adult counterparts, although there are no transitional data for late fetal life and infancy [33].

The absorption of Cbl as measured by one or more techniques was abnormal in the four reported [9–12] and two unreported cases where absorption was determined. (It was said to be normal in one partially reported case [28], but no details were given.) The impairment is not a consequence of Cbl deficiency of the intestinal mucosa because it has persisted during remission. TC II probably combines with the Cbl coming from the lumen of the intestine within the ileal cell [34]. Thus, the absence of TC II may interrupt the normal sequence necessary for full absorption. Absorption of Cbl was, however, normal in the one person with a TC II capable of binding Cbl and reacting with anti TC II, but non-functioning in the known function of TC II, promotion of cell uptake of Cbl. The combination of these observations suggests that it is the Cbl binding function of TC II and not the interaction with TC II-Cbl cell receptors that is needed for the sequence of absorption.

The congenital defects teach much about the significance of the serum Cbl. Distinctly low levels usually mean body depletion of Cbl, but in the congenital deficiency of R binders the serum Cbl is pathologically low in spite of normal amonts of tissue Cbl [7,8]. Low levels should be predictable because about three-fourths of the serum Cbl is normally bound to R binder [17] and when none is available, the serum Cbl should be, and is, about a fourth normal [8]. Serum Cbl levels are known for ten patients with the congenital deficiency of TC II either pre-treatment or at a planned relapse. In each instance, levels always were normal or high, never low. This pattern is also predictable. Probably the total body Cbl is normal or nearly so, but the distribution is faulty. The fraction of serum Cbl bound to TC II should be, and is [15], absent when there is no fully functioning TC II, but this fraction is, at most, about one-fourth of the total serum Cbl [17], too small to drop the serum Cbl into a subnormal range. It is interesting that the serum Cbl is normal in the congenital defects of both Cbl-dependent enzyme activities [25,32]. Here there is no impairment of absorption or transport of Cbl but in the synthesis of Ado Cbl and Me Cbl. In the one case of a TC II that bound Cbl but was otherwise non-functional, the serum Cbl was much increased (Table 1). Total, apo, and holo TC II were all increased. Probably the abundant TC II attracted Cbl to the serum while the impaired attachment to TC II-Cbl receptors permitted it to remain in the circulation.

Experiences with these congenital defects suggest that Cbl leaves the tissues in a free form and is distributed between the plasma carriers in proportion to the numbers of open binding sites. The pattern is further modified by rates of removal which differ between TC II-Cbl and R-Cbl. Of course, if body Cbl is depleted there is less available to be bound to the carriers and serum Cbl falls. The opposing concept, that the serum Cbl represents an active excretion of already bound Cbl gets no support from the above and there is further contrary evidence. If the R-Cbl of serum under usual circumstances represented holo enzymes which contained Cbl being released from tissues, one or more forms of Cbl would be missing in the deficiency of R binder. The forms of Cbl in the serum of a subject, W.B., with a congenital deficiency of R binders [8] were measured by thin-layer chromatography and bioautography. There was binding of both Ado Cbl and Me Cbl to the TC II present (Table 3). Both Me Cbl and Ado Cbl were also observed in the serum of a child deficient in TC II [28].

The response to treatment of those congenitally deficient in TC II has been instructive. While the administration of folic acid is not recommended, some affected children did receive it with improvement in the hematologic manifestations. This response supports the concept that in Cbl deficiency the ultimate disturbance which is responsible for the megaloblastic process relates to folate metabolism in some unknown way. More positive information comes from the response to pharmacologic amounts of Cbl. Free Cbl is generated in the circulation [15] and free Cbl when present in adequate amounts will enter human cells to be converted to coenzyme forms [15]. This latter point was well documented in a series of definitive

TABLE 3
Forms of Cbl in the Serum of Congenital Deficiency of R Binder

	Values as pg/ml – ( ) = % distribution			
	Ado Cbl	Me Cbl	OH Cbl	CN Cbl
W.B. – No R Binding	16 (57)	12 (43)	0	0
Simultaneous Control	148 (19)	458 (59)	101 (13)	70 (9)

studies which included fibroblasts from a child deficient in TC II [29]. Thus, the function of TC II seems to be an enhancement of Cbl uptake by cells, enabling the small amounts of Cbl that are available in nature to satisfy needs.

An attempt to devise an orderly nomenclature for the disorder of plasma transport is given in Table 4. For the proteins we prefer the terms transcobalamin II (TC II, TC 2) and R-binder of Cbl (R CBL). The names for the respective genes follow logically and once a standard nomenclature is agreed upon for the alleles conveying a normal TC II [2,3] or R [4], these can be added. The same nomenclature would be difficult to apply to all but one of the abnormal TC II variants because the method used to study normal alleles is not applicable. Instead, we suggest using three letters of the place of first description. Our suggestion conforms to recent guidelines for gene nomenclature [35] and can be added to or altered readily.

Diagnostic suggestions are also implicit in Table 4. Confusion often comes from what at first glance seems to be an incompatability between levels of serum Cbl and clinical expression. It is in the deficiency of R binder that the serum Cbl is low, but the tissues are replete and the person is asymptomatic in respect to Cbl metabolism. Detection may be at any age and usually comes from an independent reason for measuring serum Cbl. In the deficiency of TC II there is life-threatening megaloblastic pancytopenia, infection, mouth ulcers, and gastrointestinal symptoms, but the serum Cbl is normal. If the disorder is not treated early in infancy there is no second chance. Measurement of the capacity of TC II or R to bind Cbl added *in vitro* is the most widely available approach to the diagnosis [36,37]. Serum must be collected before injection of large amounts of Cbl because if binding sites are thus blocked, the protein will not be detected even when present in normal amounts. Saliva is a good source for the search for R binder because there are normally large amounts and contaminating TC II is very low. Thus, the UBBC is essentially a measure of apo R. Specialized techniques such as measure of immunoreactivity, holo R and TC II, and the functions of TC II are best left to laboratories when they are used frequently.

CONCLUSIONS

The observations from the study of congenital disorders of plasma Cbl transport support to different degrees several concepts of transport and metabolism of Cbl.

1. R binder of Cbl is nonessential.
2. The R binder of several body tissues and fluids is determined by a single genetic locus with at least two codominant alleles.
3. Transcobalamins II (TC II)
   a. is essential under natural circumstances of Cbl intake, but

TABLE 4
Parameters of Serum Cbl and Proposed Nomenclature
For Congenital Disorders of Plasma Cbl Transport

Genotype	Phenotype	Serum Cbl pg/ml	Carrier Protein as Detected by: Cbl Binding	Carrier Protein as Detected by: Immunoreactivity
Congenital Deficiency of R Binder [7,8]				
RCBL*BNX/ RCBL*BNX	RCBL BNX	Low	Nil	Reduced
RCB*BNX/ RCBL	RCBL	N	N	Sl. Red.
Variant of TC II Deficiency with no detectable TC II [9-12,14]				
TC2*SEA/ TC 2*SEA	TC2 SEA	N	Nil	Nil
TC2*SEA/ TC2	TC2	N	Reduced	Reduced
Variant of Immunoreactive TC II, but No Binding [13]				
TC2*DEN/ TC 2*SEA	TC2 DEN-SEA	N	Nil	Reduced
TC2*DEN/ TC2	TC2	N	Reduced	N
Variant of Increased, Nonfunctioning TC II [16]				
TC2*CZA/ TC2*CZA	TC2 CZA	Increased	Increased	Increased

BNX = Bronx, SEA = Seattle, DEN = Denver, CZA = Cardeza
The table gives only combinations already studied. Presumably homozygous TC II Denver would be expressed by symptoms, normal serum Cbl, normal immunoreacting TC II, but no binding of Cbl to TC II.

b. can be circumvented by the administration of very large amounts of free Cbl.
c. TC II promotes entry of small amounts of Cbl into cells, but
d. does not seem to be needed for Cbl metabolism after internalization.
e. TC II is necessary for complete Cbl absorption, and
f. takes part in the recycling of Cbl as well as in the distribution postabsorption.
g. possibly all tissues do not depend on TC II to the same degree, but more likely
h. the needs of rapidly dividing cells are more immediate and current while other cells can go longer without recent TC II-Cbl uptake.
i. TC II is determined by a single genetic locus with several codominant alleles, some of which are expressed as abnormal forms of TC II.

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